REMARKS

Rejections under 35 U.S.C. 112, first paragraph

The Office Action rejects claims 197-230 because the claims allegedly are not sufficiently enabled throughout their scope. In particular, the Office Action maintains that the specification does not adequately enable:

- Cross-species nuclear transfer; and
- Nuclear transfer in which the donor genetic material is not contained in a donor nucleus.

In response to the rejection, Applicants have limited the claims to same species nuclear transfer, and have further limited the claims to nuclear transfer in which the donor genetic material is contained in a nucleus. Applicants have not limited the claims to nuclear transfer in which the donor genetic material is contained in a donor nucleus because it is well known among skilled workers that chromosomes can be transferred to recipient cells, and that such transfers can be accomplished without damage to the chromosome. See, e.g.,Compton et al., Nucleic Acids Research, 1999, Vol. 27, No. 7, pp. 1762-1765 (copy attached)..

Rejections under 35 U.S.C. 112, second paragraph

The Office Action rejects claims 221 and 223-225 because these claims allegedly do not further limit claim 197, because claim 197 is drawn to a method of producing a cloned nonhuman NT embryo, and claims 221 and 223-225 specify the production of an animal. As requested in the Office Action, Applicants have rewritten these claims as methods of producing a nonhuman cloned human mammal using the embryo made by the method of claim 197.

Rejections under 35 U.S.C. 102

The Office Action further rejects claims 197, 199, 200, 206, 208, 209, 212, 214, 220, 222 and 227 under section 102(b) for allegedly being anticipated by Collas et al (1992) Biol. Reprod. 46, 492-500. Collas et al disclose the use of blastomeres in a nuclear transfer process. The

reference indicates that the blastomeres were incubated in aphidicolin before the nuclear transfer, and that this incubation yielded donor cells that were arrested in G1.

In response to the rejection, Applicants have amended claim 197 to require that the G1 arrest of the donor cell be initiated by a CDK2 inhibitor. Because the aphidicolin employed in the Collas reference is not a CDK2 inhibitor, but instead synchronizes the cell cycle by inhibiting DNA polymerases, claim 197 is not anticipated by the Collas reference.

Applicants have also added a new series of claims beginning with claim 231 that are limited to nuclear transfer processes in which somatic cells are employed as the donor cells. Because Collas employed blastomeres as the donor cells, Collas does not anticipate these claims.

Rejections of claims 197-230 under 35 U.S.C. 103

The Office Action also rejects various claims for allegedly being obvious over a combination of references including (1) Collas (1992), (2) Stice (US 5,945,577), (3) Wakayama et al. (1998) Nature 394, pages 369-374, (4) Cibelli et al. (1998) Science 280, pages 1256-1259, (5) Yang et al. (1992) Biol Reprod. 46, suppl. 1, page 117, abstr. 268, (6) Campbell et al. (1996) Nature 380, 64-66, (7) Collas et al. (1992) Biol. Reprod. 46, 492-500, and (8) Alessi et al. (1988) Exp. Cell Res. 245, 8-18.

Notably, none of the references teaches the use of roscovitine or other CDK2 inhibitor to arrest a donor cell in G1 before performing nuclear transfer, as recited in the pending claims. The Office Action alleges that "Alessi teaches that olomucine and roscovitine are CDK2 inhibitors and arrest human fibroblasts in G1." According to the Office Action, a skilled worker would have been motivated to use aphidicolin to arrest donor cells in G1 prior to nuclear transfer in view of Collas's teachings, and further would have been motivated to substitute a CDK2 inhibitor for aphidicolin in view of Alessi et al.

The Office Action fails to set forth a prima facie case of obviousness because it fails to cite a suggestion in the art to substitute a CDK2 inhibitor for aphidicolin in a nuclear transfer process. Alessi investigated CDK2 inhibitors for purely experimental reasons because "the identity of the protein substrates of these kinases is far from being completely discovered." (P. 8, col. 2). Alessi also investigated CDK2 inhibitors because "such a class of molecules may

represent a novel tool for inhibition of tumor cell growth." There is absolutely no suggestion in Alessi that CDK2 inhibitors should be substituted for the polymerase inhibitors of Collas in a nuclear transfer process. Alessi actually suggests just the opposite because Alessi suggests using CDK2 inhibitors to kill cells in a cancer treatment regimen because "such a class of molecules may represent a novel tool for inhibition of tumor cell growth." A skilled worker would not be motivated to use a chemical that kills cells or that "inhibits tumor cell growth" in a process that is designed to promote life such as nuclear transfer.

In addition, there is no expectation of success that a CDK2 inhibitor could be substituted for a DNA polymerase in a nuclear transfer process. A skilled worker could arrest a donor cell in G1 using a variety of techniques and a variety of chemical treatments. However, without knowing what harmful side effects a CDK2 inhibitor would have on other biological pathways in the cell cycle, whether the CDK2 inhibitor would affect the activation process for the fused embryo, and whether the CDK2 inhibitor would have an affect on the eventual division and parturition of the embryo after nuclear transfer, the nuclear transfer scientist would have no expectation that a CDK2 inhibitor would actually work. Once again, Alessi teaches away from the use of a CDK2 inhibitor in a nuclear transfer process when he states that "the identity of the protein substrates of these kinases is far from being completely discovered." (Alessi, p. 8, col. 2). A skilled worker would not be motivated to use a CDK2 inhibitor when he does not even understand what protein substrates CDK2 kinases regulate, and what biological pathways might be unwittingly impacted.

Aphidicolin is a DNA polymerase inhibitor that halts the cell cycle at the border between the G1 and S phases. In contrast, CDK2 inhibitors work upstream of DNA polymerases, and actually recruit DNA polymerases after forming a complex with cyclin. CDK2 inhibitors and polymerase inhibitors thus act by completely distinct biological mechanisms. The bare fact that both classes of compounds will arrest donor cells in G1 would not lead a skilled worker to believe that both classes of compounds could be used in a nuclear transfer process. The Office Action asserts that a skilled worker would have been motivated to use aphidicolin in a nuclear transfer process because Collas showed that aphidicolin would actually increase nuclear transfer efficiencies. This point further shows that a skilled worker would not have been motivated to

substitute a CDK2 inhibitor for aphidicolin in a nuclear transfer process, because the skilled worker would not have made such a substitution unless he expected the CDK2 inhibitor also to increase nuclear transfer efficiencies. However, the cited references do not show that a skilled worker would even expect nuclear transfer to be possible using CDK2 inhibitors, much less that the CDK2 inhibitor could increase the nuclear transfer efficiencies.

The prior art also teaches away from substituting CDK2 inhibitors for DNA polymerase inhibitors because, even if a skilled worker were motivated to use aphidicolin in nuclear transfer processes as alleged in the Office Action, the skilled worker would not be inclined to substitute for aphidicolin a compound that affects processes upstream from aphidicolin in the cell cycle. It would generally be believed among scientists that the arrested cell should be as close to S phase as possible to allow the donor cell to enter S phase in the oocyte and undergo DNA synthesis as needed for the embryo to develop and cleave into two cells. It would thus be counterintuitive to substitute a CDK2 inhibitor for aphidicolin.

Rejection of claims 231-263 under 35 U.S.C. § 103

Applicants have also added a new series of claims beginning with claim 231 that are limited to nuclear transfer processes in which somatic cells are employed as the donor cells. Because Collas employed blastomeres as the donor cells, Collas does not anticipate these claims.

The Office Action states that Stice et al. disclose a nuclear transfer process wherein the donor cell is a somatic cell, and that a skilled worker would have been motivated to use Colla's G1 arrest procedure in Stice's method because Collas reported improved rates of development using the G1 arrested donor cells. However, the bare fact that Collas showed that a G1 arrest agent would improve the development rates of oocytes using blastomeres as the donor cell, would not motivate a skilled worker to use the G1 arrest agent with somatic cell nuclear donors.

As the examiner is aware, blastomeres have a very different cell cycle than somatic cells. Somatic cells have a longer G1 phase in proportion to the S, G2 and M phases, whereas blastomeres have a rather short G1 phase in proportion to S, G2 and M phases. Because of these differences, a skilled worker would have no expectation that arresting somatic cells in G1 would

improve development rates similarly to the improvements that Collas observed when using blastomeres as donor cells.

If the examiner has any questions about the pending claims or the arguments presented herein, she is invited to contact the undersigned at 404-572-3513. The Commissioner is authorized to charge any additional fee or credit any overpayment associated with this submission, to Deposit Account No. 11-0980.

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